Complete Summary

GUIDELINE TITLE

AACE medical guidelines for clinical practice for management of menopause.

BIBLIOGRAPHIC SOURCE(S)

American Association of Clinical Endocrinologists. AACE medical guidelines for clinical practice for management of menopause. 1999 Nov-Dec. 12 p. [62 references]

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Menopause

GUIDELINE CATEGORY

Evaluation
Management

CLINICAL SPECIALTY

Endocrinology
Internal Medicine
Obstetrics and Gynecology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To provide a reference source for the evaluation and treatment of the menopausal state.

TARGET POPULATION

Menopausal and perimenopausal women.

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

- History and physical examination
- Laboratory studies (ie., baseline serum chemistry studies and complete lipid evaluation, hormonal evaluation)

Treatment:

- Hormone replacement therapy
    - Estrogens
        - Conjugated equine estrogens
        - Esterified estrogens
        - Estropipate and other estrone sulfate preparations
        - Micronized 17ß -estradiol
        - Ethinyl estradiol
        - Transdermal estradiol patches (various brand names)
        - Vaginal estrogenic preparations including a vaginal ring
    - Progestins
        - Medroxyprogesterone acetate (MPA)
        - Levonorgestrel
        - Norethindrone
        - Micronized progesterone
        - Depo-Provera
    - Oral contraceptives
    - Androgens and anabolic agents
- Bisphosphonate and other agents for osteoporosis.
- Other agents: Clonidine, Bellergal, fluoxetine or other selective serotonin reuptake inhibitors for autonomic symptoms.

MAJOR OUTCOMES CONSIDERED

- Relief of subjective and objective symptoms
- Prevention of osteoporosis
- Prevention of cardiovascular disease
- Prevention of dementia
- Prevention of carbohydrate intolerance

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The guideline developer searched the literature using the database MEDLINE (U.S. National Library of Medicine), as well as hand searches of the primary and secondary published literature.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review
Review of Published Meta-Analyses

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not applicable

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Not stated

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Summarized by the National Guideline Clearinghouse (NGC):

History

The patient's current symptoms should be carefully assessed. The most common symptoms attributed to menopause in women are vasomotor instability, insomnia, depression, nervousness, dysphoria, asthenia, decreased libido, dyspareunia, palpitations, formications (crawling sensations), mastalgia, paresthesia, myalgia, headache, and arthralgia.

The history should routinely include the following information:

- A detailed chronologic reproductive history including time of menarche, gravidity and parity, history of breast-feeding, gynecologic surgical history, and a detailed menstrual history.
- History of hormonal treatment, including contraceptives (orally administered, injectable, or implant), estrogens, progesterone, and androgens
- Detailed sexual history, including frequency of intercourse, ease of arousal, libido, orgasm, and dyspareunia
- Symptoms of pelvic floor relaxation and bladder dysfunction
- Bone or joint pain, arthritis, fractures, and osteoporosis
- Loss of height
- General current and past personal medical history, family history, and social history
- History of achlorhydria and lactose intolerance
- History of weight fluctuations, physical activity, and exercise tolerance
- Quality-of-life assessment, psychiatric history, premenopausal mood disorders, premenstrual dysphoria (for example, premenstrual syndrome), and cognitive functioning
- Family history, especially early menopause, cardiovascular disease, osteoporosis, cancer, and dementia
- Dietary history with emphasis on intake of sodium, vitamins (especially vitamin D), and calcium
- Medications (for example, corticosteroids)
- Understanding of fears and expectations surrounding menopause

Physical Examination

As part of the comprehensive physical examination, particular attention should be paid to the following:

- Posture (signs related to osteoporotic compression changes), gait (flexibility), muscle tone, coordination, height, and body proportions
- Body mass index, body composition, and waist circumference
- Breast examination

- Pelvic examination, which should include size and shape of the uterus and adnexal structures, evaluation of estrogenic status of the vaginal mucosa, elasticity and thickness of the vaginal wall (discharge, atrophy), integrity of the pelvic floor (cystocele, rectocele), and levator ani function
- Eyesight and hearing acuity (in terms of fracture risk and quality of life)

Laboratory Studies

Baseline serum chemistry studies, including complete lipid evaluation, should be performed. In addition, a thorough hormonal evaluation and other baseline investigations should be undertaken.

Gonadotropin levels (FSH) should be determined. The measurement of FSH is the key laboratory test for the diagnosis of menopause. Interpretation of FSH levels in menopausal and perimenopausal women is discussed in greater detail in the guideline document.

Estrogen, progesterone, androgen, and thyrotropin levels should also be determined, when indicated.

The following studies may be necessary or useful at the time of initial assessment:

- Papanicolaou ("Pap") smears
- Mammography
- Bone density determinations
- Assessment of endometrium, when indicated
- Pelvic ultrasound screening, when indicated

Hormone Replacement Therapy (HRT)

In a woman with a uterus, HRT must include an estrogen and a progestational agent because the use of estrogen alone can produce endometrial hyperplasia or carcinoma (or both). In the absence of a uterus, a progestational agent is unnecessary.

Estrogens

The following are the most commonly used estrogens:

- Conjugated equine estrogens
- Esterified estrogens
- Estropipate and other estrone sulfate preparations
- Micronized 17ß-estradiol
- Ethinyl estradiol
- Transdermal estradiol patches (various brand names)
- Vaginal estrogenic preparations including a vaginal ring

In addition, other available preparations such as estrogen pellets, gels, creams, intranasal sprays, or injections (for example, Depo-Estradiol) have been used. The major differences among these formulations are in the mode of absorption and

the pharmacokinetics. Few, if any, clinically significant qualitative differences exist between free and conjugated estrogens.

The oral and transdermal routes are the most frequently used. Patients acceptance and prior experience are the major factors in determining the preferred route of delivery.

The dosage of estrogen used to initiate HRT should be individualized because it is strongly dependent on age of the patient and various other factors.

Progestins

After a hysterectomy, progestins are unnecessary. In a woman with an intact uterus, the endometrium must be protected against hyperplasia and possible progression to dysplasia and carcinoma by the use of progestational agents.

The classic regimen consists of medroxyprogesterone acetate (MPA) used for 10 to 14 days each month. Levonorgestrel, norethindrone, or micronized progesterone can also be used for this purpose.

In menopausal and postmenopausal women whose autonomic symptoms (hot flashes and sweats) are not relieved by tolerable doses of estrogen, supplemental clonidine, Bellergal (a combination of ergotamine, belladonna alkaloids, and phenobarbital), or fluoxetine or a similar selective serotonin reuptake inhibitor can be used. In addition, Depo-Provera, a microcrystalline suspension of MPA can be used in special circumstances, as for selected menopausal patients with breast cancer.

Low-dose oral contraceptives are widely used in perimenopausal women to regulate menses as well as to control fertility. There is no longer concern regarding increased cardiovascular risk in women older than 35 to 40 years of age. There is no upper age limit for the use of these formulations. They are being used more frequently in postmenopausal women because of better control of menstrual bleeding in comparison with the aforementioned regimens. Other methods of cycle control with contraceptive formulations are discussed in the guideline document.

Androgens and Anabolic Agents

Androgen replacement has been practiced as long as estrogen replacement. Today, four general groups of women are considered candidates for estrogen + androgen therapy:

1. women who have had their ovaries removed
2. those who have not experienced relief of vasomotor symptoms with a maximally tolerable dose of estrogen
3. those at risk for osteoporosis in whom other modalities are not satisfactory or suitable
4. those with unsatisfactory sexual function, especially loss of libido

Because no consensus exists about the use of androgen therapy, the potential benefits and risks should be explored for each patient.

Patient Compliance

Adherence of the patient to treatment recommendations is fundamentally dependent on the physician-patient dialogue, as outlined in the following 10 basic principles of menopause management:

- Recognize that menopause causes a permanent deficiency of estrogen.
- Understand the system, organ, and tissue consequences of this deficiency.
- Appraise the benefits and risks of the treatment options.
- Educate women about the nature and consequences of permanent estrogen deficiency.
- Engage in interactive discussion about the benefits and risks of therapeutic intervention. Provide printed materials and, if possible, videotapes to reinforce the verbal information. Address specifically the issue of breast cancer, which is uppermost in many women's minds.
- Implement an acceptable course of action.
- Evaluate promptly the real and perceived consequences of the intervention.
- Reevaluate the real and perceived benefits as well as the disadvantages and risks at regular intervals.
- Be aware of and discuss information and misinformation patients may have received through such sources as media reports, advocacy groups, and well-meaning friends.
- Raise the level of information, concern, and involvement in the medical community.

Management when HRT Cannot Be Used:

Available alternatives when HRT is contraindicated or not tolerated include the following options for prevention and/or treatment of osteoporosis:

- Selective estrogen receptor modulators (i.e., raloxifene)
- Alendronate, a bisphosphonate
- Calcitonin
- Calcium, vitamin D, and exercise

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

All women should consider hormone replacement therapy (HRT) not only as essential replacement of missing hormones but also as a type of preventive medicine. The risks and benefits of HRT should be individualized on the basis of quality-of-life considerations and a personal risk assessment, with consideration of cardiovascular, osteoporotic, dementia, and cancer risk factors. Therefore, the mission of the clinical endocrinologist should be to educate women and fill this void relative to the health benefits of HRT and to convey the proper balance of risk-versus-benefit information.

Prevention of Osteoporosis

The role of HRT in the prevention of osteoporosis is extensively addressed in another AACE clinical practice guideline, "Prevention and Treatment of Postmenopausal Osteoporosis" (Endocrine Practice 1996 Mar-Apr;2[2]:155-71). In summary, epidemiologic evidence indicates that most women exposed to estrogen therapy for 7 to 10 years or longer have a 50% or greater reduction in the incidence of osteoporotic fractures. Long-term estrogen users may still experience senile bone loss, and continued estrogen therapy may be less likely to arrest bone loss or prevent fractures in women after age 75 years. A pooled estimate of the relative risk of hip fracture comparing estrogen users with nonusers is 0.7 (95% confidence interval).

Prevention of Cardiovascular Disease

- Several meta-analyses of observational studies have demonstrated a 35 to 50% lower relative risk (RR) of cardiovascular mortality in HRT users relative to nonusers.
- In contrast, a large, randomized, placebo-controlled study of HRT for the prevention of recurrent coronary artery disease (CAD) found no beneficial effect of a HRT regimen during a 4-year period, with respect to nonfatal myocardial infarction and CAD deaths.
- The difference between the results of the randomized, placebo-controlled study, which showed no benefit of HRT on preexisting CAD, and the numerous other observational studies that have shown very large decreases in relative risk remains speculative.

Prevention of Dementia

A meta-analysis of the observational studies of the effect of estrogen therapy on the risk for developing dementia supports a 29% decreased risk among estrogen users.

Prevention of Carbohydrate Intolerance

Various studies have shown that HRT is associated with a decrease in the likelihood of developing diabetes by a factor of nearly 5, improves blood glucose control, and is associated with a decrease in the risk of myocardial infarction in

women with diabetes (RR=0.51; 95% confidence interval [CI], 0.22 to 1.15 overall and RR=0.78; 95% CI, 0.56 to 1.08 per year of HRT use).

POTENTIAL HARMS

- There is a small but statistically increased risk of thromboembolism (estimated at 3/10,000 per year), usually occurring within the first year of therapy, that applies to all forms of estrogen.
- In women who use orally administered estrogens, a statistically increased risk of cholelithiasis has been found.
- Although the issue of breast cancer risk and HRT is unlikely to be resolved for a variety of reasons, women should know that of 55 observational studies of this question between 1974 and 1996, 90% failed to demonstrate an increased risk of breast cancer.
- Side effects of progestational compounds are difficult to evaluate and will vary with the progestational agent administered. Some women experience premenstrual-tension-like symptoms, including mood swings, bloating, retention of fluids and sleep disturbance.
- Side effects of excessive androgen therapy, include seborrhea, acne, hirsutism, alopecia and (in extreme cases) voice changes and clitoral hypertrophy.

Subgroups Most Likely to be Harmed:

- Women who have had documented deep vein thrombophlebitis or pulmonary embolism in the past should, most probably, not be prescribed any form of HRT.
- Undiagnosed genital bleeding necessitates diagnostic evaluation before initiation of HRT.
- Gall bladder disease may be increased by orally administered estrogens.
- Systemic lupus erythematosus and Raynaud's disease can be exacerbated by HRT.

CONTRAINDICATIONS

CONTRAINDICATIONS

A history of breast or uterine cancer is the main contraindication to hormone replacement therapy (HRT).

QUALIFYING STATEMENTS

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The guideline consists of recommendations for the clinical management of menopause and is intended for use by physicians to support their treatment of women's reproductive health issues. The American Association of Clinical Endocrinologists (AACE) recognizes that this guideline should be used in conjunction with the best clinical judgment and the patient's individual needs.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

American Association of Clinical Endocrinologists. AACE medical guidelines for clinical practice for management of menopause. 1999 Nov-Dec. 12 p. [62 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1999 Nov-Dec

GUIDELINE DEVELOPER(S)

American Association of Clinical Endocrinologists - Medical Specialty Society

SOURCE(S) OF FUNDING

Wyeth-Ayerst Laboratories provided an educational grant that supported the publication and distribution of this guideline.

GUIDELINE COMMITTEE

Not stated

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

This guideline will be revised and updated periodically to reflect the latest developments in the management of menopause.

GUIDELINE AVAILABILITY

Electronic copies: Available from the American Association of Clinical Endocrinologists (AACE) Web site.

Print copies: Available from the American Association of Clinical Endocrinologists (AACE), 1000 Riverside Avenue, Suite 205, Jacksonville, FL 32204.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- AACE 2001 medical guidelines for clinical practice for the prevention and treatment of postmenopausal osteoporosis. Endocrine Practice; 2001 Jul-Aug;7(1):293-312

Electronic copies: Available from the American Association of Clinical Endocrinologists (AACE) Web site.

Print copies: Available from the American Association of Clinical Endocrinologists (AACE), 1000 Riverside Avenue, Suite 205, Jacksonville, FL 32204.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on October 28, 1999. The information was verified by the guideline developer on February 22, 2000.

Date Modified: 11/8/2004